

¹⁷31. A method according to claim ¹²11 wherein said mammal is a sheep.

²⁰32. A method according to claim ¹⁸16 wherein said mammal is a sheep.

²²33. A mammal according to claim ²¹19 wherein said mammal is a sheep.

³³34. A mammal according to claim ³⁰27, wherein said mammal is a sheep.--

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cont.

REMARKS

Reconsideration of the application in view of the above amendments and following remarks is requested. With entry of this amendment, claims 1-34 are now in the case. Claims 16, 19 and 20 have been amended, and new claims 30-34, directed to certain preferred embodiments of applicants' invention, have been added. Support for these amended and added claims is found within the application as filed. No new matter has been added.

Claims 2, 12, and 17 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner maintains that the specification fails to provide an enabling disclosure for the full scope of what is claimed. The Examiner believes that the specification fails to provide an enabling disclosure for the preparation of any and all transgenic animals because the artisan would not have accepted, *a priori*, that one could have produced fibrinogen in transgenic cattle. The Examiner cites Houdebine as indicating that transgene expression in milk had not been observed in cattle and that regulatory sequences must be tested empirically, leading to unpredictable success and failure. Wall is cited as disclosing a lack of predictability for transgene products in livestock.

Applicants respectfully traverse this rejection. Methods for producing transgenic cows were known in the art prior to applicants' filing date, and such methods have been disclosed by applicants. For example, Clark et al. (U.S. Patent No. 5,366,894, filed Nov. 22, 1991 and its PCT counterpart, WO 88/00239, cited in applicants' specification at page 12) disclose a method for producing heterologous proteins in the milk of transgenic animals. Within the disclosed method, cattle are a preferred host species (paragraph bridging columns 3-4 of U.S. 5,366,894). Rosen (U.S. Patent No. 5,304,489, filed Oct. 24, 1990) discloses a method of targeting specific genes to the mammary gland. The method is disclosed as being useful in "any mammal" (column 3 at lines 37-38), including cattle (column 9 at lines 65-66).

As to the expectation of success with transgenic cattle, applicants first wish to direct the Examiner's attention to Fig. 1 of the Houdebine article. This figure includes cattle among "transgenic mammals of various sizes which are expected to express the foreign gene in their milk." The Clark and Rosen patents discussed above provide further evidence of the expectations of those skilled in the art at applicants' filing date.

It is respectfully submitted that Houdebine does not teach, as indicated by the Examiner, that "transgene expression had not been observed in cattle." Table 6 of Houdebine discloses in the third line that human lactoferrin cDNA has been expressed in a transgenic cow. A more comprehensive review of the available literature shows not only that skilled practitioners expected transgenic cows to be a viable source of recombinant proteins, but that transgenic cattle had been produced before applicants' filing date. For example, on June 8, 1990 the *New York Times* reported that four gene-altered calves had been developed in Texas, and that transgenic cattle had also been developed in Canada and Europe. The *Times* further reported that in June 1986, Dr. Robert Church at the

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University of Calgary developed a calf that expressed a human interferon gene. The work of Dr. Church is also reported by Van Brunt (*Bio/Technology* 6:1149-1154, 1988; see page 1154, left-hand column). The April 21, 1994 edition of *Biotechnology News* reported that GenPharm Inc. had about 20 lactoferrin-producing cows. In 1991, Krimpenfort et al. (*Bio/Technology* 9:844-847, 1991; disclosed in applicants' specification at pages 11-12) disclosed a new method for generation of transgenic dairy cattle. From 21 pregnancies, two transgenic calves had been obtained. In the same issue of *Bio/Technology*, Bialy (*Bio/Technology* 9:786, 788, 1991) reports on advances in transgenic livestock production and discloses that one of the calves produced by Krimpenfort et al., a male named "Herman", "showed the presence of intact lactoferrin DNA in all tissues tested." It was later reported (*BioWorld International*, May 1, 1996, page 7) that "Cows sired by the transgenic bull Herman already are producing lactoferrin in their milk."

Copies of references cited above that are not already of record in this case are enclosed herewith.

The Examiner cited the Wall reference in support of the alleged unpredictability of transgenic production in livestock. However, Wall's statement that "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predictable" (emphasis added) does not preclude patentability under § 112. Absolute predictability is not required. Experimentation is permitted, so long as that experimentation is not undue. In the present case, the level of skill in the art was very high, the methods to practice the invention were known, and considerable experimentation to produce transgenic animals was routine. The latter point is confirmed by Table 1 of Wall, which discloses that, for example, 5,424 sheep embryos were injected and transferred to obtain 556 offspring, 8.3% of which were transgenic. As disclosed by Wall (Table 1) and

Houdebine (Table 8), the frequency of transgenesis is comparable in sheep and cattle. One skilled in the art would therefore recognize the need to produce a large number of embryos in order to establish a herd, and such experimentation was and is routine in this area. Methods for carrying out such experimentation and analysis are disclosed in applicants' specification at pages 25-33 and elsewhere. Such experimentation is certainly not undue, when those skilled in the art routinely produce a large number of embryos and screen many offspring to obtain founder animals. The nature of the technology requires such screening.

The Examiner cited Wall as disclosing that "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies." Applicants respectfully submit that this statement does not support the instant rejection. Applicants have shown that biocompetent fibrinogen is produced by livestock. In the instant case, mouse studies were predictive.

Applicants are also enclosing herewith a Declaration Under 37 C.F.R. § 132 of Will H. Eyestone. In his Declaration Dr. Eyestone discusses experiments directed to the production of transgenic animals and the expression of the transgenes by those animals, and concludes that, as of applicants' filing date, one skilled in the art would have been able to generate transgenic cattle carrying expression units for the three chains of human fibrinogen with the expectation that at least some female members of the resulting line would produce milk containing biocompetent fibrinogen. Dr. Eyestone's declaration confirms that the skilled artisan would have accepted that one could have produced fibrinogen in transgenic cattle.

Claims 1-8 and 11-29 stand rejected under 35 U.S.C. § 103 as being unpatentable over Meade et al., Archibald et al., and Roy et al. on the grounds that the

claims are not limited to biocompetent fibrinogen and are therefore obvious.

This grounds of rejection is traversed in part and overcome in part. Claim 1 as filed recites the step of breeding said offspring to produce female progeny that express said first, second and third DNA segments and produce milk containing biocompetent fibrinogen encoded by said segments (emphasis added)

Similar recitations are contained in claims 11 and 27 as filed. Claims 16 and 19 have been amended to recite that the fibrinogen is biocompetent. Claim 20 has been amended to recite, "wherein female progeny of said mammal express said DNA segments in a mammary gland to produce biocompetent fibrinogen." Support for these amendments is found within the application as filed, such as at pages 3-5 and in claim 27. The remaining claims include such limitations by virtue of their dependence on one of claims 1, 11, 16, 20 or 27. The cited references neither teach nor suggest the production of biocompetent fibrinogen in transgenic animals.

Claims 9 and 10 stand rejected under 35 U.S.C. § 103 as being unpatentable over Meade et al., Archibald et al., and Roy et al. as applied to claims 1-8 and 11-29, and further in view of Chung et al.

As noted above, with entry of this amendment all claims now recite "biocompetent" fibrinogen. Applicants submit that the amended claims are patentably distinguished over the cited combination of references.

On the basis of the above amendments and remarks, applicants believe that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner

feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,
Ian Garner et al.



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Enclosures:

Petition and Fee for Extension of Time (in duplicate)
Amendment Fee Transmittal (in duplicate)
7 References
Declaration of Will H. Eyestone Under
37 C.F.R. § 1.132
Postcard